

# PATENT SPECIFICATION

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NO DRAWINGS



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## COMPLETE SPECIFICATION.

### Improvements in or relating to Solid, Water-Dispersible Pharmaceutical Compositions.

We, DAGRA N.V., a Dutch Body Corporate of Diemen, Netherlands, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel process for the preparation of non-hygroscopic water-dispersible pharmaceutical compositions.

According to the present invention we provide a process for the preparation of solid non-hygroscopic, water-dispersible pharmaceutical compositions wherein a crystalline sugar is mixed with 1–5% by weight of highly dispersible silica and/or calcium silicate, the mixture is impregnated with a hot aqueous solution of citric acid and/or tartaric acid, the impregnated mixture is rapidly dried to a moisture content of 0.2–0.3% by weight, the product obtained is ground and thereafter one or more pharmaceutical active components are added. The powders so obtained can be pressed to tablets, pills and dragees or products prepared therefrom for dispersion in water by the user.

The crystalline sugar may, if desired, contain one or more synthetic sweetening agents, such as sodium cyclamate or saccharine. Rapid drying (which tends to prevent or reduce inversion of sucrose) may advantageously be effected by means of a hot stream of air.

The grinding of the dried mixture is advantageously so effected as to give a particle size of approximately 0.15–0.3 mm.

When the dried and ground product is mixed with the pharmaceutical active component or components other ingredients may conveniently be added, e.g. colouring,

flavouring, odour-producing, effervescent, thickening dispersing emulsifying or lubricating agents. Thus, for example, a physiologically acceptable powdered dye of appropriate fineness, one or more liquid or powdered flavours or if a powder having effervescent properties is required sodium bicarbonate may be added. In the case of water dispersible powders if one wants to give the liquid to be prepared from the powder a somewhat thickened character, this may be effected by means of the addition of powdered thickening agent such as dried gum arabic, gum tragacanth or carboxymethylcellulose.

The powders produced by the process of the invention, in contradistinction to previously proposed water dispersible powders containing sugar and citric or tartaric acid, e.g. common lemonade powders, do not quickly attract moisture. If the starting materials described above are simply mixed without using the above procedure the acids, in the presence of small quantities of moisture, may then invert the sucrose, as a consequence of which hygroscopic mixtures are formed. Under such conditions, pharmaceutical substances which are sensitive to moisture therefore decompose with loss of activity, and often with production of bad tastes and odours (e.g. as with thiamine). Where bicarbonate is present, of course, carbon dioxide is evolved and further water is produced. By preparing the compositions according to the process of the invention it is possible to obtain powders with stable therapeutic and organoleptic properties which are, as a consequence thereof, especially suitable for use in pediatrics. Moreover, where a dye is incorporated, the fact that the white powders disperse in water with

formation of colour is interesting and attractive to children.

In order that the invention may be well understood we give the following examples by way of illustration only:—

#### Example 1

A mixture was prepared of 1.08 kg sodium cyclamate, 60 g sodium saccharinate, 1.50 kg highly dispersed silica (average particle size 15  $\mu$ ) and 46.7 kg crystalline sugar. This mixture was impregnated with a solution of 4.68 kg tartaric acid in 2.4 litres distilled water at 60–80°C.

Subsequently drying was effected in a stream of air of 50°C during 20 minutes, to give a moisture content of 0.2% by weight. The mass was ground in a cross centrifugal mill to an average particle size of 0.15 mm and subsequently mixed with 2.40 kg sodium bicarbonate, 1.20 kg gum arabic powder, 600 g powdered orange flavour, 300 g powdered lemon flavour, 36 g sunset yellow and vitamins to the following dosages per 5 g final product:

25	2000 I.U. vitamin A
	1 mg vitamin B <sub>1</sub>
	1 mg vitamin B <sub>2</sub>
	5 mg nicotinamide
	0.5 mg calcium d-pantothenate
30	0.1 mg vitamin B <sub>6</sub>
	0.6 mcg vitamin B <sub>12</sub>
	20 mcg folic acid
	50 mg vitamin C
	400 I.U. vitamin D <sub>3</sub>

After six months there were found in the composition kept at 37°C:

35	1980 I.U. vitamin A
	0.95 mg vitamin B <sub>1</sub>
	0.98 mg vitamin B <sub>2</sub>
40	4.92 mg nicotinamide
	0.48 mg calcium d-pantothenate
	0.1 mg vitamin B <sub>6</sub>
	0.59 mcg vitamin B <sub>12</sub>
	18.8 mcg folic acid
45	48.7 mg vitamin C moisture content

0.4%  
(Vitamin D<sub>3</sub> cannot chemically be determined in this mixture).

When the above starting materials were simply mixed there were found after six months' keeping at 37°C:

50	640 I.U. vitamin A
	0.58 mg vitamin B <sub>1</sub>
	0.92 mg vitamin B <sub>2</sub>
55	4.70 mg nicotinamide
	0.36 mg calcium d-pantothenate
	0.08 mg vitamin B <sub>6</sub>
	0.22 mcg vitamin B <sub>12</sub>
	11.0 mcg folic acid
60	28.0 mg vitamin C moisture content

5.6%

#### Example 2

A mixture was prepared of 54 g sodium cyclamate, 3 g sodium saccharinate, 75 g calcium silicate and 2.30 Kg crystallized sugar. This mixture was moistened with a solution of 225 g citric acid in 120 cc distilled water at 80°C.

Subsequently drying was effected in a stream of air at 40–50°C during 15–20 minutes to give a moisture content of 0.3%. The mass was ground to an average particle size of 0.3 mm and subsequently mixed with 120 g sodium bicarbonate, 120 g gum arabic powder, 30 g powdered cherry flavour, 3 g liquid vanilla essence, 2 g amaranth, 75 g acetyl salicylic acid (needle-shaped, fine crystals) and 600 mg sodium lauryl-sulphonate.

Immediately after preparation, 125.2 mg acetyl salicylic acid per 5 g of mixture were found; moisture content 0.35%. After keeping during 6 months at 17°C this fell to 123.8 mg.

In a composition prepared from the above starting materials by simple mixing, after 6 months' keeping at 17°C, only 108.2 mg acetyl salicylic acid per 5 g were found; the moisture content amounted to 2.4%.

#### Example 3

4.58 kg of the ground premix described in example 1 was mixed with 240 g sodium bicarbonate, 1.10 kg ascorbic acid, 30 g powdered orange flavour, 60 g powdered lemon flavour and 4 g tartrazine.

After 6 months' keeping at 37°C, 98.8% of the vitamin C originally present was recovered, as against 83.0% in a composition prepared by simple mixing.

#### WHAT WE CLAIM IS:—

1. A process for the preparation of solid non-hygroscopic water dispersible pharmaceutical compositions in which a crystalline sugar is mixed with 1–5% by weight of highly dispersed silica and/or calcium silicate, the mixture then being impregnated with a hot aqueous solution of citric acid and/or tartaric acid and the impregnated mixture rapidly dried to a moisture content of 0.2 to 0.3% by weight and ground, the ground mixture then being mixed with one or more pharmaceutical active substances.

2. A process as claimed in claim 1 in which the crystalline sugar has also mixed therewith a synthetic sweetening agent.

3. A process as claimed in claim 2 in which the sweetening agent is sodium saccharine or sodium cyclamate.

4. A process as claimed in any of claims 1–3 in which the said finely ground mixture is mixed with one or more colouring, flavouring, odour-producing, effervescent, thickening, dispersing, emulsifying or lubricating agents in addition to said pharma-

ceutical active substance or substances.

5 5. A process as claimed in claim 4 in which the said finely ground mixture is mixed with a bicarbonate as an effervescent agent.

10 6. A process as claimed in claim 4 or claim 5 in which the finely ground mixture is mixed with gum arabic, gum tragacanth or carboxymethyl cellulose as thickening agent.

7. A process as claimed in any of the preceding claims in which the fine grinding of the dried mixture gives a product of particle size approximately 0.15 to 0.3 mm.

15 8. A process as claimed in any of the preceding claims in which the rapid drying of the said impregnated mixture is effected in a hot air stream.

20 9. A process as claimed in claim 8 in which the air stream is at 50°C.

10. A process as claimed in any of the preceding claims in which the pharmaceutical substance comprises one or more vitamins or acetyl salicylic acid.

25 11. A process as claimed in claim 1 substantially as herein described.

12. A process as claimed in claim 1 substantially as herein described with reference to any of the Examples.

13. A non-hygroscopic, water-dispersible pharmaceutical composition containing one or more sugars, highly dispersed silica and/or calcium silicate and citric acid and/or tartaric acid whenever prepared by a process as claimed in any of the preceding claims. 30 35

14. A process for the preparation of a non-hygroscopic, water-dispersible premix of use in the preparation of pharmaceutical compositions wherein a crystalline sugar is mixed with 1—5% by weight of highly dispersed silica and/or calcium silicate, the mixture being impregnated with a hot aqueous solution of citric acid and/or tartaric acid and the impregnated mixture rapidly dried to a moisture content of 0.2—0.3% by weight and ground. 40 45

15. A non-hygroscopic, water-dispersible premix whenever produced by a process as claimed in claim 14.

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